IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 2663
Steven M. RUBEN	Art Unit: 1644
Appl. No.: 10/662,429	Examiner: HUYNH, PHUONG N.
Filed: September 16, 2003	Atty. Docket: 1488.1890003/EJH/SAC
For: **Apoptosis Inducing Molecule I**	

Declaration of Reiner L. Gentz
Ruben Exhibit #58

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Paper No. _____

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES
(Administrative Patent Judge Sally Gardner Lane)

STEVEN M. RUBEN

Junior Party,
(Application No. 08/816,981),

v.

STEVEN R. WILEY
and RAYMOND G. GOODWIN

Senior Party,
(Patent No. 5,763,223).

Patent Interference No. 105,077

DECLARATION OF REINER L. GENTZ

Ruben EXHIBIT 2058
Ruben v. Wiley et al.
Interference No. 105,077
RX 2058

DECLARATION OF REINER L. GENTZ

I, Reiner L. Gentz, declare and state as follows:

1. I was employed by Human Genome Sciences, Inc. (HGS) in the position of Senior Vice President, Protein Development. I joined HGS in December 1993 as Director, Protein Expression and Purification, which position I held until May 1997. From May 1997 to December 2000, I served as Vice President, Protein Development. I have been asked by patent counsel for HGS to describe the importance of the AIM-I project to the company and my role and that of Dr. Guo-Liang Yu in producing and characterizing AIM-I during the time period from 1995 through March 14, 1996.

2. Human Genome Sciences, Inc. (HGS) was founded in 1992 as a start-up company in the emerging field of genomic-based pharmaceuticals. During the period from 1992 to March 14, 1996, HGS was a small, young, rapidly-growing company when compared to other companies developing pharmaceutical products. Nevertheless, by January 20, 1995, HGS had already sequenced thousands of human cDNAs and deduced the sequence of a large number of proteins for potential product development. Compared to this large number of potential products, HGS had a relatively small work force for carrying out the experiments that such development requires. Only a handful of potential products were designated high priority and thus received a great deal of experimental attention in the first four years of company existence. AIM-I was one of the select few molecules designated as a high priority project and chosen for development.

3. It was known to HGS scientists at least by January 20, 1995, that the TNF ligand family was involved in regulating immune cell proliferation and activity effected through the

binding of each ligand to one or more TNF receptor family members. It was also known to HGS scientists at this time that AIM-I, cloned and isolated first at HGS by Steven Ruben, was a member of this TNF ligand family. Thus, to better understand the role and mechanism of AIM-I apoptotic activity, we attempted to identify such TNF receptor family members to ultimately determine which receptors did and did not bind AIM-I. Also key to this analysis of AIM-I function was to compare and contrast the expression patterns of the various members of both the TNF ligand (*e.g.*, TNF gamma, delta, and epsilon) and TNF receptor (*e.g.*, TR1, TR2, and TR3) families, and thereby identify the likely target receptor(s) and target cell line(s) for AIM-I. Therefore, work carried out by HGS and SmithKline Beecham ("SB") scientists from at least January 20, 1995 through March 1996 on various TNF ligand and receptor family members, such as TNF gamma, delta, and epsilon, and TR1, TR2, and TR3 all contributed to further elucidating the biological function of AIM-I.

4. Because of the great interest in the TNF ligand family, including in particular AIM-I, a joint program was established between HGS and SB (the "HGS/SB Joint Program") to commit greater resources toward developing these ligands and their receptors as potential therapeutic agents. I managed HGS's involvement in this HGS/SB Joint Program. Thus, during the time period from at least January 20, 1995 through March 1996, a great deal of activity was ongoing among the members of the large group participating in the HGS/SB Joint Program in an effort to identify, characterize and develop members of the TNF ligand and TNF receptor families. The large number of scientists named on the distribution list for the agenda (RE76, pages 1-2) and the minutes (RE71) for the joint HGS/SB meeting of October 18, 1995 reflects the exceptional amount of resources that were committed to the development of AIM-I and the other TNF ligand and receptor family members during the time period spanning at least

January 20, 1995 through March 1996. Thus, in addition to the work being conducted by Steven Ruben and Ann Kim in the Ruben laboratory, the HGS/SB Joint Project included activities by Jian Ni, who was a post-doc in my laboratory, Guo-Liang Yu and his assistant Lily Xing, and myself, each of HGS; and Alem Truneh, Edward R. Appelbaum, his assistant Edward Dul, and Kong B. Tan, among others, each of SB.

5. I recall discussing with Dr. Ruben around the time he identified AIM-I, and certainly by January 20, 1995, that because of the high degree of homology of AIM-I to TNFα and FasL, HGS should pursue the development of AIM-I based therapeutics, including anti-AIM-I antibodies, for example for treatment of autoimmune diseases, or the AIM-I protein itself, for example, for treatment of cancer. A decision was made in HGS at least by January 20, 1995 to pursue the development of AIM-I therapeutics as a matter of high interest in HGS's interdepartmental program. HGS's program involved a variety of discovery platforms in place at HGS to obtain as much information about AIM-I in the quickest manner possible to guide the development of AIM-I therapeutics. Several of the discovery platforms applied to AIM-I, such as expression in a variety of systems such as E. coli, baculovirus, and CHO cells, Northern analysis, the fluorescence *in situ* hybridization to detect chromosomal location of the AIM-I gene and the indirect immunofluorescence studies of AIM-I protein were utilized virtually exclusively in development of therapeutics and diagnostics from molecules of high interest. Such "high interest" molecules, including AIM-I, represented a miniscule fraction of the hundreds of molecules that were being identified as part of HGS's gene discovery program from 1994 to 1996.

6. One discovery platform used for developing AIM-I therapeutics was the protein expression platform. Under my direction, the Protein Expression Group at HGS spent extensive

efforts to develop an insect expression system for AIM-I as part of a TNF ligand and TNF receptor family expression program. Insect cell expression is useful for production of large quantities of protein having a eukaryotic glycosylation pattern. The Sf9 system (baculovirus) is one of three major, routine expression systems that have been used at HGS to determine optimal expression systems. I communicated with Dr. Ruben regarding the significant efforts in 1995 that my group took to express AIM-I in the insect cell system. In addition to expression of AIM-I protein, the HGS Protein Expression Group that I directed was evaluating expression systems for TNF ligand family member TNF gamma (also referred to as VEGI or HUVE091), and TNF delta. Because of the high degree of similarity among TNF ligand family members, we anticipated that information regarding suitable expression systems for TNF gamma and delta would also be useful to determine the most suitable approach to express AIM-I protein for the development of AIM-I therapeutics. Among the members of the Protein Expression Group working on elucidating suitable expression conditions of AIM-I and other TNF ligand family members in 1995 and 1996 under my supervision were Dr. Timothy Coleman, Dr. Guo-Liang Yu, Solange Gentz (then known as Solange Lima), Lily Xing, and Markus Buergin.

7. As noted above, Dr. Guo-Liang Yu was a scientist at HGS during the time period from 1995 through 1996, who was a member of the HGS/SB Joint Program that I managed. During this time period, he both directly carried out and supervised his research assistant Lily Xing's carrying out of a large number of experiments analyzing members of the TNF ligand family, including AIM-I, as well as three new TNF-like ligands, HUVEO91 (TL1 or TNF gamma), HPDD012 (TNF epsilon) and HLTBT71 (TNF delta) as well as TNF-receptor like HTTBN61, a TNFR p55 homolog (TR3) which was considered at that time to be a possible

receptor for AIM-I, particularly in light of its intracellular death domain. These experiments are recorded in Dr. Yu's Notebooks 143 (RE61) and 481 (RE63) and are summarized below.

8. During Dr. Yu's tenure at HGS, I coordinated with him on the development of the TNF family ligand members, including participating in a number of meetings with him and Dr. Ni to discuss the progress of these projects. During the 1995 to 1996 time period, I was personally aware of Dr. Yu carrying out experiments on TNF ligand and receptor family members, primarily to clone and express cDNAs encoding several of these proteins, that are reflected in his Notebooks 143 and 481. I also know that it was the general business practice at HGS during the 1994 to 1996 time frame for a scientist to contemporaneously date an entry in his or her notebook upon entering it, and for the scientist's supervisor to sign and date a scientist's notebook to attest to having read and understood (*i.e.*, "witnessed") all the preceding entries in the notebook dating back to the previously witnessing, as I did with notebook 279 of Solange Gentz, then known as Solange Lima (*see e.g.* RE69, pages 33 and 42). Based on my personal knowledge of the research that Dr. Yu was carrying out in the 1995 to 1996 time frame, the HGS company policy of laboratory notebook record keeping, and my having read Dr. Yu's laboratory Notebooks 143 and 481, I conclude Dr. Yu carried out activities as described below.

9. On August 21, 1995, Dr. Yu designed oligos for use in various tasks regarding TNF-like ligands, HPDDO12 (TNF epsilon) and HLTBT71 (TNF delta) (RE61, page 122).

10. On August 25, 1995, Dr. Yu carried out a PCR experiment to amplify sequences of TNF delta, epsilon, and gamma. On August 31, 1995, Patrick J. Dillon, Dr. Yu's supervisor, witnessed and signed his notebook (RE61, page 123).

11. On September 4, 1995, Dr. Yu analyzed PCR products of TNF gamma for cloning into CHO vectors (RE61, page 124).

12. On September 27, 1995, Patrick Dillon witnessed and signed his notebook (RE61, page 130).

13. On October 4, 1995, Dr. Yu prepared for cloning the full-length TNF epsilon by PCR from the HPD library (RE61, page 131).

14. On October 5, 6, 9, and 10, 1995, Dr. Yu carried out a DNA capture experiment to isolate, transform into E. coli, and identify by PCR clones of TNFRp55 (TR3) and TNF5, another TNF ligand family member. (RE61, pages 132-134).

15. On October 16, 1995, Dr. Yu designed an experiment to construct a TNF gamma-IL6 signal fusion. On October 17, 1995, Patrick Dillon witnessed Dr. Yu's notebook. (RE61, page 135).

16. On October 18, 1995, Dr. Yu, Dr. Jian Ni, and I attended a joint meeting with SB at SB's facility in Pennsylvania. (RE76, page 2; RE71).

17. On October 23, 1995, Dr. Yu reported the sequence analysis of four HTTBN61 clones. He also designed a new oligo for an IL6/TNF gamma fusion construct (RE61, page 136).

18. On October 25-27, Dr. Yu analyzed PCR products for engineering a TNF delta expression construct (RE61, pages 137-138).

19. On November 7, 1995, Dr. Yu performed a PCR on several HPD library samples using primers designed for TNF delta (RE61, page 139).

20. On November 10, 1995, Dr. Yu made new primers for TNF delta with a BamHI site and performed another PCR (RE61, page 139).

21. On November 20, 1995, Patrick Dillon witnessed Dr. Yu's notebook (RE61, page 140).

22. On November 20, 1995, Dr. Yu performed a RACE (rapid amplification of cDNA ends) PCR reaction for HTTBN61, a TNFR p55 homolog (TR3) (RE61, page 141).

23. On November 21, 1995, Dr. Yu gel-purified some of the reaction products from the November 20, 1995 RACE reaction (RE61, page 142).

24. On November 28, 1995, Dr. Yu analyzed the results but observed no specific products (RE61, page 142). Also on this date, the TNF delta his tag construct sequence was verified, and the DNA given to the protein expression group (RE61, Page 143).

25. On or about December 12, 1995, Dr. Yu entered the results of Northern analysis for the HTTBN61 TNFR into his notebook (RE61, page 146).

26. On January 16, Dr. Yu placed an order for chromosome mapping TNF delta (HLTBT71), as recorded in IRIS, the HGS electronic notebook for memorializing and archiving, for example, chromosome mapping and nucleotide sequencing orders (RE62). I have personally entered information into and retrieved reports from IRIS and know that it preserves the ordering date of such mapping and sequencing orders.

27. On January 24, 1996, Dr. Yu performed an endothelial cell proliferation assay to test the activity of two "EDAP" (TNF gamma) clones and one TNF delta clone (RE63, page 2).

28. On February 26, 1996, Peter R. Young of SB sent to me an agenda for a meeting scheduled for February 28, 1996. The agenda listed the SB speakers would be Peter Young, Terry Porter, Yen-Sen Ho and K.B. Tan and that other attendees would be Sally Lyn, Michele Gorczya and Alem Truneh. Peter Young was slated to discuss, for example, the expression of AIM-I ("TL2"). K.B. Tan was slated to discuss RNA blot analysis of TNF receptor family members and TNF ligand family members, including AIM-I. Significantly, Yen-Sen Ho was slated to discuss development of an apoptosis assay (RE84).

29. On March 8, 1996, Dr. Yu entered into his notebook the results of an SDS PAGE analysis of induction of AIM-I recombinant protein expression (RE63, page 6).

30. On March 12, 1996, Dr. Yu designed an experiment to isolate the 5' end sequence of clone HTTBN61, also then referred to as DDCR, for death domain containing receptor (I RE63 page 8).

31. On March 13, 1996, Dr. Yu designed an experiment to clone several TNF ligand family members (EDAPΔ2, EDAPΔ3, AIM2Δ1 and AIM2Δ2) into the pQE60 vector. On March 14, 1996, Patrick Dillon witnessed Dr. Yu's notebook (I RE63, page 9).

32. As noted above, Lily Xing was a scientist at HGS during the time period from June 1995 through March 1996, who performed a large number of experiments analyzing members of the TNF ligand family, including AIM-I, and the TNF receptor family (*see e.g.* ¶7, above), under the direct supervision of Dr. Yu, and under my general direction and control. These experiments are recorded in Ms. Xing's Notebook 351 RE129 and are summarized below.

33. During Ms. Xing's tenure at HGS, during the 1995 to 1996 time period, I was personally aware of Ms. Xing's carrying out experiments on TNF ligand and receptor family members, primarily to clone and express cDNAs encoding several of these proteins, as reflected in her Notebook 351. I also know that it was the general business practice at HGS during the 1995 to 1996 time frame for a scientist to contemporaneously date an entry in his or her notebook upon entering it, and for the scientist's supervisor to sign and date a scientist's notebook to attest to having read and understood (*i.e.*, "witnessed") all the preceding entries in the notebook dating back to the previously witnessing. Based on my personal knowledge of the research that Ms. Xing was carrying out in the 1995 to 1996 time frame, the HGS company policy of laboratory notebook record keeping, and my having read Ms. Xing's laboratory Notebook 351, I conclude Ms. Xing carried out activities as described below.

34. Ms. Xing recorded the experiments that she carried out during the period from February 1996 through the middle of March 1996 in her notebook 351. During this period, Dr. Yu signed and dated her work in notebook 351, according to the practice described above, as follows:

Page	Date
120	February 9, 1996
125	February 20, 1996
130	February 29, 1996
135	March 8, 1996

35. On February 8-9, 1996, Ms. Xing measured the concentration of various primers for TNF receptors and ligands, including AIM-I ("Trail"), and performed PCR reactions to amplify them RE129 pages 119-121).

36. On February 12-16, 1996, Ms. Xing digested, ligated, transformed, blotted, picked colonies, measured DNA concentration, and performed PCR for a number of TNF ligand and receptor constructs, including AIM-I ("HTPA (Trail)") RE129 pages 121-125).

37. On February 20-23, 1996, Ms. Xing continued preparation of nine TNF ligand and receptor constructs, including AIM-I ("HTPA (Trail)") RE129 pages 126-128).

38. On February 25-29 and March 1, 1996, Ms. Xing continued construct preparation of various TNF ligand and receptors, including AIM-I ("HTPA") RE129 pages 128-131).

39. On March 4-8, 1996, Ms. Xing continued construct preparation of various TNF ligand and receptors, including TNFR HTTBN61 and AIM-I ("HTPA" or "HTPAN08S04"). Induction of protein expression was also performed and visualized on protein gels RE129 pages 132-135).

40. On March 10-15, 1996, Ms. Xing prepared an HT4 construct (HT4CC72) for induction of protein expression. Ms. Xing also gave samples of HPDDO12 and AIM-I to Jian Ni on March 14, 1996 RE129 pages 135-139).

41. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application captioned above or any patent issuing thereupon.

Date: 6/23/2004

Reiner L. Gentz

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